SGLT2i Increase Endogenous Glucose Production: That's Good News!

Andrea Giaccari

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In this issue of *Diabetes Care*, Alatrach et al. (1) present an investigation into the effects of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on endogenous glucose production (EGP) in patients with type 2 diabetes during an 8-h fast and after an oral glucose load. The study included 48 patients divided into four groups: dapagliflozin (DAPA), exenatide (EXE), DAPA/EXE, and placebo (PCB). The first protocol evaluated EGP response to therapy after an 8-h tracer infusion. Results showed that EGP decreased with PCB and EXE and remained unchanged with DAPA and DAPA/EXE. In protocol 2, patients were restudied with a state-of-the-art 5-h double-tracer oral glucose tolerance test. EGP decreased with PCB and EXE, while with DAPA and DAPA/EXE the decrease in EGP was attenuated. The authors accurately measured insulin and glucagon concentrations, the two main regulators of EGP. However, neither hormonal changes nor their ratio completely justified the blunted suppression of EGP by DAPA, prompting the authors to suggest that additional factors must be involved.

The results of the study are in line with others by DeFronzo and colleagues (2,3) and Ferrannini et al. (4), which also demonstrated an increase in EGP during use of SGLT2i. In 2014, Merovci et al. (2) and Ferrannini et al. (4), in two separate articles and with two different SGLT2i, both reported an increase in EGP in patients with type 2 diabetes during inhibition of SGLT2. The main aim of the study by Merovci et al. (2) was to determine whether reduction of plasma glucose with DAPA could improve insulin-mediated tissue glucose disposal and insulin secretion in patients with type 2 diabetes (through relief from glucose toxicity) (3), while Ferrannini et al. (4) found that empagliflozin-induced glycosuria increased EGP despite improved insulin secretion and sensitivity in patients with type 2 diabetes.

To maintain euglycemia, tissue glucose uptake occurring during the fasting state is compensated for by gluconeogenesis and glycogenolysis, both of which take place mainly in the liver (5). In gluconeogenesis, glucose is formed chiefly from lactate and amino acids but also from oxalacetate, the main entry point for the oxidation of acetyl-CoA. In the first hours of fasting, glucose is produced mainly by glycogen breakdown in the liver. Over longer periods of fasting, when there is no more glycogen, glucose is produced solely by gluconeogenesis. The increase in gluconeogenesis consumes oxalacetate, pushing acetyl-CoA to form ketones, the only alternative substrate to glucose for the brain. As the fasting state progresses, glucose concentration slowly declines (especially in type 2 diabetes), finally activating renal gluconeogenesis.

In the fasting state, a normal subject metabolizes glucose at the rate of $\sim$2 mg·kg^{-1}·min^{-1}. In other words, every 30 min a quantity equal to that of all the glucose present in the blood is renewed. Thus, even if the glucose concentration remains relatively stable, uptake and production flows are intense, underlining the crucial role of their regulation.

How is EGP regulated? While insulin is the key regulatory hormone suppressing glucose production and glucagon is a major stimulator of glucose appearance, other players are also involved: hormones (catecholamines, cortisol, etc.), the central nervous system (6), free fatty acids (FFA) (7), and glucose concentration itself. Decades ago, we showed that hyperglycemia per se inhibits EGP, both gluconeogenesis and glycogenolysis, even with stable insulin and glucagon. Importantly, this inhibition is lost in the partially pancreatectomized rat (a model of glucose toxicity) (8,9) independent of insulin and glucagon concentrations. The absence of this inhibition therefore is mainly responsible for increased EGP and thus for hyperglycemia, at least in this model. This is a model, however, in which diabetes is induced by partial pancreatectomy and thus all alterations in the liver (and skeletal muscle) are consequent to chronic hyperglycemia, i.e., glucose toxicity. In a 1998 study, Mevorach et al. (10) confirmed these data in humans. It is interesting that, at least in our murine model, the regulation of gluconeogenesis and glycogenolysis is different. In fact, glycogenolysis remains partially sensitive to inhibition by hyperglycemia, in contrast to gluconeogenesis,

Center for Endocrine and Metabolic Diseases, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, and Università Cattolica del Sacro Cuore, Rome, Italy

Corresponding author: Andrea Giaccari, andrea.giaccari@unicatt.it

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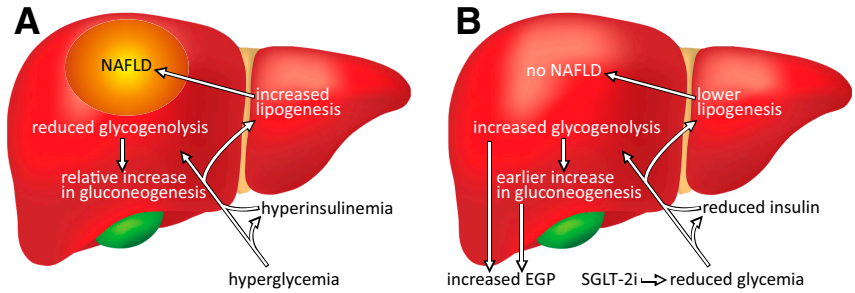

Figure 1—Glucose regulation of EGP and effects of SGLT2 inhibition. *A*: Hyperglycemia normally inhibits EGP, mainly through the reduction of liver glycogenolysis. This effect is partially lost in diabetes, in which hyperglycemia also causes a relative increase in gluconeogenesis. The increased hepatic glucose uptake, together with the concomitant hyperinsulinemia, stimulates hepatic lipogenesis, increasing the risk of NAFLD. *B*: The reduction of hyperglycemia (through SGLT2i-induced glycosuria) and insulin concentrations allow an increased glycogenolysis and a subsequent early increase in gluconeogenesis, with a concomitant reduction of lipogenesis (and reduced risk for NAFLD). EGP is also increased. This reduces the amount of glucose diverted to lipogenesis and does not increase plasma glucose, as excessive glucose is immediately lost with urine.

hence the well-known increase in gluconeogenesis in diabetes (Fig. 1*A*) (9).

In the study by Alatrach et al. (1), the subjects treated with DAPA had comparable levels of insulin and glucagon, but glycemia was lower because glucose was being lost through urine. The hyperglycemia inhibition was removed, and therefore EGP increased (Fig. 1*B*). Further, islet cells sensed lower glucose concentrations (due to glycosuria) and reacted accordingly, reducing insulin and increasing glucagon secretion. Finally, the increase in glucagon led to ketogenesis (not ketoacidosis, which occurs only when insulin levels are very low). It is interesting that insulin inhibits EGP not only through its effect on the liver but also through the inhibition of lipolysis (4); in fact, FFA stimulate EGP.

Increased EGP usually has negative connotations, being a result of low insulin levels and hepatic insulin resistance. This becomes particularly significant in insulin therapy. One of the main differences between endogenous and exogenous insulin is that the former has greater concentrations in the portal vein and therefore inhibits EGP. Exogenous insulin, on the other hand, has low portal vein concentrations; its effect on EGP is probably mainly due to the inhibition of lipolysis. It would therefore be tempting to use an (exogenous) insulin able to exert its main effect on the liver, and this was the initial purpose of pegylated insulin. Unfortunately, pegylated insulin has been found to induce nonalcoholic fatty liver disease (NAFLD) (11).

Glucose entering the liver (in the postprandial state) is mainly utilized to form glycogen and FFA through lipogenesis. As glycogen stores are maintained at high levels in diabetes (due to the suppressing effect of hyperglycemia), lipogenesis prevails, leading to the frequent occurrence of NAFLD in diabetes (Fig. 1*A*). Thus, mechanisms that push greater quantities of glucose into the liver are not always positive but actually cause one of the comorbidities of type 2 diabetes. In contrast, mechanisms that reduce the entry of glucose into the liver or, better still, push glucose out of the liver can improve NAFLD (Fig. 1*B*). To date, a number of studies have shown that treatment with SGLT2i can reduce NAFLD (12), so the increase in EGP, induced by SGLT2i, can be viewed in a positive light.

In the past, diabetologists considered glycosuria a negative factor because it meant hyperglycemia. Today, we know that glycosuria can also be a positive aspect because it reduces glycemia (and glucose toxicity). We have always considered an increase in EGP undesirable, but, in fact, it removes calories from the liver and reduces glucolipid toxicity, including NAFLD. That is definitely good news!

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References

1. Alatrach M, Agyin C, Solis-Herrera C, et al. Dapagliflozin impairs the suppression of endogenous glucose production in type 2 diabetes following oral glucose. Diabetes Care 2022;45:1372–1380
2. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509–514
3. Merovci A, Mari A, Solis-Herrera C, et al. Dapagliflozin lowers plasma glucose concentration and improves β-cell function. J Clin Endocrinol Metab 2015;100:1927–1932
4. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499–508
5. Litwak G. Human Biochemistry. Amsterdam, Elsevier, 2018
6. Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med 2002;8:1376–1382
7. Lewis GF, Vranic M, Harley P, Giacca A. Fatty acids mediate the acute extrahepatic effects of insulin on hepatic glucose production in humans. Diabetes 1997;46:1111–1119
8. Giaccari A, Rossetti L. Predominant role of gluconeogenesis in the hepatic glycogen repletion of diabetic rats. J Clin Invest 1992;89:36–45
9. Giaccari A, Morviducci L, Pastore L, et al. Relative contribution of glycogenolysis and gluconeogenesis to hepatic glucose production in control and diabetic rats. A re-examination in the presence of euglycaemia. Diabetologia 1998;41:307–314
10. Mevorach M, Giacca A, Aharon Y, Hawkins M, Shamoon H, Rossetti L. Regulation of endogenous glucose production by glucose per se is impaired in type 2 diabetes mellitus. J Clin Invest 1998;102:744–753
11. Davies MJ, Russell-Jones D, Selam J-L, et al. IMAGINE 2 Study Investigators. Basal insulin peglispro versus insulin glargine in insulin-naïve type 2 diabetes: IMAGINE 2 randomized trial. Diabetes Obes Metab 2016;18:1055–1064
12. Pradhan R, Yin H, Yu O, Azoulay L. Glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors and risk of nonalcoholic fatty liver disease among patients with type 2 diabetes. Diabetes Care 2022;45:819–829